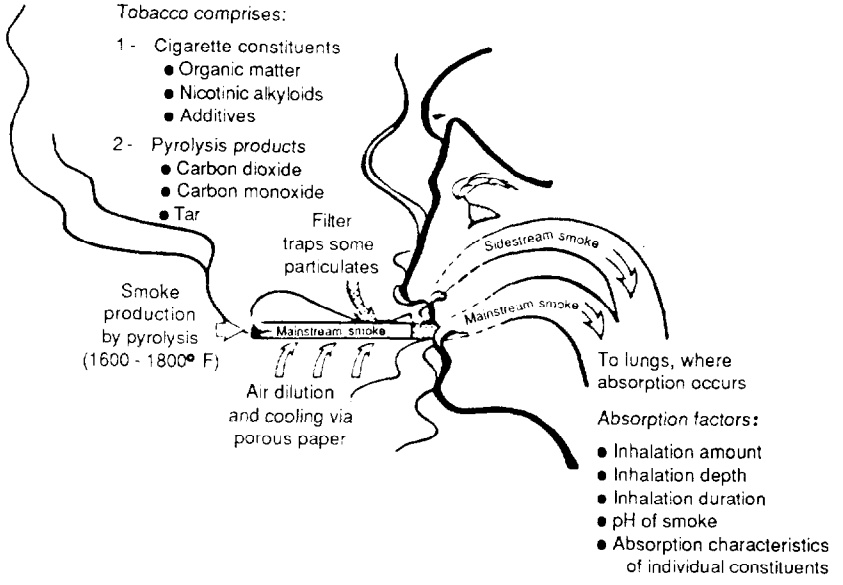

FIGURE 1.—Production and fate of cigarette smoke constituents

NOTE: Description of complexity of process by which nicotine is extracted from cigarette. Amount of nicotine ultimately absorbed is as much a function of smoker behavior as of cigarette characteristics.
SOURCE: Henningfield (1984).

appearance; *cigarette smoking is no exception.* The behavior of lighting, smoking, and extinguishing cigarettes, including puffing and inhaling, also becomes regular in smokers over time. The measurement techniques that permit such conclusions, however, must address a complex behavior. There are many variables (e.g., number of puffs, depth of inhalations) that might change and thereby affect the intake of tobacco smoke and its various constituents (e.g., nicotine, tar, carbon monoxide (CO)). As shown in Figure 1, the process of producing cigarette smoke constituents itself is complex (see US DHEW 1979; US DHHS 1981, for a more thorough discussion of these factors). This complexity emphasizes the importance of the use of careful measurement and multiple measures to ensure accurate characterization of cigarette smoking.

Quantification of cigarette smoking behavior has improved with the development of automated measurement techniques. These techniques permit the measurement of puffing and inhalation both in the laboratory (Gust, Pickens, Pechacek 1983; Epstein, Dickson, Stiller et al. 1982; Creighton, Noble, Whewell 1978; Herning, Hunt,

Jones 1983; Henningfield and Griffiths 1979; Puustinen et al. 1987) and outside the laboratory (Henningfield et al. 1980; Grabowski and Bell 1983). Puffing behavior is generally measured by having subjects smoke through cigarette holders that measure air flow by use of either temperature-sensitive thermistors (Gritz, Rose, Jarvik 1983; Fagerström and Bates 1981) or pressure-sensing transducers (Henningfield and Griffiths 1979; Gust, Pickens, Pechacek 1983a; Rawbone et al. 1978). Inhalation behavior has been measured by a variety of techniques, including mercury strain gauge pneumography (Rawbone et al. 1978; Herning et al. 1983), head- and arms-out whole-body plethysmography (Adams et al. 1983), and impedance (Nil, Buzzi, Bättig 1986) and inductive plethysmography (Herning, Hunt, Jones 1983; Tobin and Sackner 1982; Tobin, Jenouri, Sackner 1982). Other methods include the use of inert gas radiotracers to determine the amount of smoke inhaled (Sheahan et al. 1980; Woodman et al. 1986) and a sensor for directly measuring the concentration of smoke particles in the holder before puffing (Jenkins and Gayle 1984).

These procedures have proved to be valuable and reliable methods of measuring smoking behavior (Woodman et al. 1984; Herning, Hunt, Jones 1983). Comparisons of data obtained when simply observing smokers to data obtained when using the mechanical devices indicate that such automated measuring techniques are valid. Such comparisons reveal consistent findings on measures such as number and duration of puffs and even of patterns of puffing within cigarettes (Henningfield and Griffiths 1979; Griffiths and Henningfield 1982). However, other research suggests that the devices may alter certain characteristics of smoking such as intensity of puffing (Tobin and Sackner 1982; Ashton, Stepney, Thompson 1978; Ossip-Klein, Martin et al. 1983). In addition, some smoking behaviors, such as blocking the ventilation holes of filters of low-yield cigarettes (which can markedly influence nicotine and tar intake from the cigarette) are thwarted by the use of a cigarette holder. Nonetheless, such measurements are useful and appear to provide valid means of evaluating the effects of specific experimental manipulations.

Measurement of the intake of cigarette smoke constituents may also be obtained by analysis of various biological fluids (saliva, urine, or blood) and expired air. Chapter II reviewed the methods and practical issues of using such specimens to assess resulting levels of nicotine, cotinine (a nicotine metabolite), CO, and other tobacco-associated compounds (see also Jarvis et al. 1987; Benowitz 1983).

Use of the methods described above has led to a much better understanding of how cigarettes are smoked and factors that affect intake of smoke constituents such as CO and nicotine. In addition, these methods permit conclusions regarding which aspects of smok-

ing are most robust across individuals, which aspects are strongly influenced by pharmacologic factors, and which aspects appear to be determined by other factors. Some of these findings are reviewed in subsequent sections.

Characterization of Cigarette Smoking Behavior

Although the process of smoking a cigarette may appear to be a simple behavior, it is actually a complex series of events; a full characterization requires the measurement of a variety of interdependent indices of frequency, duration, and volume. Even the act of taking a single puff is complex. Typically, a smoker puffs a volume of smoke into the mouth, where it is held for a short period of time (Guillerm and Radziszewski 1978; Medici, Unger, Rüegger 1985). The puff itself can occur at any point during inhalation, although most commonly it occurs toward the beginning of an inhalation (McBride et al. 1984; Guillerm and Radziszewski 1978). During inhalation, the puff is diluted with ambient air which may be inhaled through the nose, the mouth, or both (Rodenstein and Stänescu 1985; McBride et al. 1984; Adams et al. 1983). The postpuff inhalation is generally longer and larger in volume than normal inspirations (Rodenstein and Stänescu 1985; McBride et al. 1984). After a variable period of breath holding, the smoker exhales, usually through the mouth (Rodenstein and Stänescu 1985).

All of the above-mentioned behavioral factors can alter nicotine absorption. The likely impact of some factors is obvious (e.g., number of puffs taken) (Kozlowski 1981); others are much more subtle (e.g., puff shape, which is a function of the air flow rate over time) (Creighton and Lewis 1978b). Analogous but distinct from puffing factors are inhalation factors (e.g., depth and duration, dilution of the puff with ambient air) which can also determine the amount of tobacco smoke constituents which are absorbed. Table 1 lists several measures of cigarette smoking that have been objectively defined and measured.

The relationships among these behavioral measures have been studied. For instance, duration and volume of puffing are generally highly correlated although they vary somewhat from smoker to smoker (Gust and Pickens 1982; Epstein et al. 1982; Adams et al. 1983; Nemeth-Coslett and Griffiths 1985; Gust, Pickens, Pechacek 1983b; Gritz, Rose, Jarvik 1983). Peak smoke flow rate has been reported to be moderately correlated with puff volume and weakly correlated with puff duration (Gritz, Rose, Jarvik 1983). The relationship between puff volume and interpuff interval is much more variable (Adams et al. 1983; Gust, Pickens, Pechacek 1983b), and puffs per cigarette and puff duration have been found to be inversely related (Lichtenstein and Antonuccio 1981).

TABLE 1.—Behavioral measures of cigarette smoking

Puffing behavior	Inhalation behavior
Puffs/cigarette	Inhalation volume
Interpuff interval	Inhalation duration
Puff duration	Breathhold duration
Butt length (weight)	Lung exposure duration
Puff volume	Percent of puff inhaled
Puff shape	
Puff flow rate (puff intensity)	
Peak flow rate (pressure)	
Latency to peak flow rate (pressure)	
Percent puffing time	

When the smoking of individual cigarettes is studied, the measures of cigarette smoking behavior and the resulting levels of biochemical markers have also been found to be highly correlated. For example, four studies found positive correlations between one or more of the behavioral measures and plasma nicotine levels (Pomerleau, Pomerleau, Majchrzak 1987; Sutton et al. 1982; Bridges et al. 1986; Herning et al. 1983). Using another approach, Zacny and associates (1987) independently varied three aspects of smoking—puff volume, inhalation volume, and lung exposure duration. They found that increases in puff volume (from 15 to 60 mL) produced proportional increases in plasma nicotine level, whereas increases in inhalation volume (from 10 or 20 to 60 percent of vital capacity) or lung exposure duration (from 5 to 21 sec) had no such effect.

CO intake (measured either from expired air or blood samples) also tends to be positively related to measures of smoking behavior, including total puff volume (Gust and Pickens 1982; Guillerm and Radziszewski 1978; Nil, Buzzi, Bättig 1984; Woodman et al. 1986) and mean puff volume (Zacny et al. 1987; Zacny and Stitzer 1986). McBride and coworkers (1984) found moderate correlations ($r = 0.36$ to 0.45) between CO boost and other measures of ventilation (tidal volume, minute ventilation, and prepuff expiratory volume). These studies illustrate some of the ways that specific aspects of cigarette smoking can affect absorption of smoke constituents. These measures have been used to scientifically describe many features of cigarette smoking. A summary of findings that have emerged from such studies is presented in the next Section.

Patterns of Puffing and Inhaling

Several studies have characterized the behavior of cigarette smoking in and outside the laboratory. The values of the most frequently measured variables are shown in Table 2. Despite a wide range of variations among studies, including differences in subject population (age, gender, smoking history, type of cigarette smoked), experimental setting, method used to collect the measurements, apparatus calibration procedures, and operational definitions of the measured variables, the findings among studies are strikingly consistent.

Over the course of smoking each cigarette there are striking consistencies from cigarette to cigarette, both within and between individuals. For example, during the smoking of a single cigarette, the duration of each puff tends to decrease and/or the time between each puff (interpuff interval) tends to increase (Graham et al. 1963; Griffiths and Henningfield 1982; Nemeth-Coslett and Griffiths 1985; Herning et al. 198l; Gust, Pickens, Pechacek 1983b; Woodman et al. 1986; Buzzi, Nil, Bättig 1985; Adams et al. 1983; McBride et al. 1984; Chait and Griffiths 1982a). These trends were also found in nonlaboratory observations by Schulz and Seehofer (1978).

Although these observations reflect a tendency to decrease overall intensity of smoking over the course of the cigarette, the specific factors which produce such effects remain to be fully elucidated. The pattern has been hypothesized to be related to the nicotine dose per puff (Rickert et al. 1983; Russell et al. 1975; Chamberlain and Higenbottam 1985), because the nicotine concentration of smoke increases as the cigarette is smoked (Kozlowski 1981). However, experimental studies suggest that within-cigarette changes in puff intensity are not a simple function of the nicotine dose per puff (Nemeth-Coslett and Griffiths 1984a,b, 1985). Furthermore, puff volume may not be controlled by the same factors as puff duration (Nemeth-Coslett and Griffiths 1985). Thus, the orderliness of the behavior may be due to a variety of factors.

Various other aspects of puffing and inhaling during the smoking of single cigarettes have been studied and provide further information that helps to characterize this complex behavioral process. For example, puff shape (puff intensity over time) (McBride et al. 1984), latency to peak puff pressure (Buzzi, Nil, Bättig 1985), and inhalation volume and duration (Adams et al. 1983) did not change over the course of smoking single cigarettes. The volume expired from puff to puff during and immediately after puffing (before inhalation) was lower for early puffs than for later puffs (Adams et al. 1983). Woodman and colleagues (1986) reported that the amount of smoke actually inhaled (range, 46 to 88 percent of puff volume) decreased proportionately with puff volume as cigarettes were smoked. Finally, significant changes from cigarette to cigarette in puff volume and

TABLE 2.—Published values of common measures of smoking

Study	Number of subjects	Puffs/ cigarette	Interpuff interval (sec)	Cigarette duration (sec)	Puff duration (sec)	Puff volume (mL)	Peak flow (mL/sec)	Inhalation volume (mL)
Rawbone et al. (1978)	12	10	41		1.8			
Rawbone et al. (1978)	9	10	35		2.1	43		
Woodman et al. (1986)	9	13	18	254	1.9	49		413
Nemeth-Coslett et al. (1986a)	8	8	64	414	1.8			
Nemeth-Coslett et al. (1986b)	8	8	47	362	1.4			
Nil, Woodson, Bättig (1986)	132	13	28		2.2	30	28	560
Jarvik et al. (1978)	9	10						
Russell et al. (1980b)	10	11	35					
Ashton, Stepney, Thompson (1978)	14		24		1.5			
Schulz and Seehofer (1978)	100	11	50		1.4			
Schulz and Seehofer (1978)	218	12	42		1.3			
Henningfield and Griffiths (1981)	8	10	39	351	1.0			
Stepney (1981)	19	13		400		38		
Bättig, Buzzi, Nil (1982)	110	13	26		2.1	40		
Epstein et al. (1982)	63	13			2.4	21		
Russell et al. (1982)	12	15	26	324	2.3	40		
Gritz, Rose, Jarvik (1983)	8	9	47		2.2	66	48	
Ossip-Klein, Martin et al. (1983)	9	8		351	1.4			
Ossip-Klein, Martin et al. (1983)	9	12		339	1.9			
Guillerm and Radziszewski (1978)	8	12	41	390	1.9	39	35	918
Gust, Pickens, Pechacek (1983b)	8	9	48	393	1.6	44		

Study	Number of subjects	Puffs/ cigarette	Interpuff interval (sec)	Cigarette duration (sec)	Puff duration (sec)	Puff volume (mL)	Peak flow (mL/sec)	Inhalation volume (mL)
Adams et al. (1983)	10		26		1.9	44		614
Moody (1984)	517	9	26	232	2.1	44		
Nil, Buzzi, Bättig (1984)	20	15	26		1.6	40	40	
McBride et al. (1984)	9	16	25	352	2.1	42		
Medici, Unger, Rüegger (1985)	17	14	19		2.2	43	31	
Burling et al. (1985)	24	12	28	330	1.7			
Nil, Buzzi, Bättig (1986)	117	13	22		2.1	42	36	450
Hughes et al. (1986b)	46	11			1.6			
Bridges et al. (1986)	108	11				56		
Puustinen et al. (1986)	11	13	22		2.3	44		
Hilding (1956)	27	10						
Mean		11	34	346	1.8	43	36	591
Median		11	28	351	1.9	42.5	35.5	560
Range		8–16	18–64	232–414	1.0–2.4	21–66	28–48	413–918

NOTE. Data were taken from the baseline phase (or placebo treatment) of studies involving an experimental manipulation, with at least eight subjects. Values are rounded off to the nearest unit, and in some cases, were calculated from other variables or estimated from data presented in figures; missing values indicate that the variable was not measured or was not presented in the published study.

inhalation volume, as well as their ratio, were reported for individual subjects over the course of a 4-hr smoking session (Herning, Hunt, Jones 1983).

Dose-Related Determinants of Tobacco Intake

As the preceding material shows, cigarette smoking is a complex but orderly behavior; it may be qualitatively and quantitatively described. Furthermore, the behavioral process of tobacco smoke self-administration substantially determines the amount of smoke that is actually consumed. Similarly, the behavior of smoking may change in response to factors related to the delivered smoke and/or nicotine dose. These interactions are described in the present section. Much of this research has addressed issues concerning the manipulation of some aspect of cigarette and/or nicotine dose level. Such data are relevant to comparing this form of drug self-administration with other forms of drug self-administration, because one of the basic findings in studies of drug-seeking behavior is that the dose may affect the behavior. For example, when the dose (quantity) of a psychoactive drug is high, fewer doses are generally taken compared to when the dose is very low (Griffiths, Bigelow, Henningfield 1980; Chapter V).

With regard to cigarette smoking, the control and measurement of cigarette dose level is more complex than is the case with most other forms of drug delivery. For example, in opioid and alcohol studies, the amount of the morphine injected and volume of alcohol consumed can be precisely measured, but cigarette smoke can vary in levels of CO, tar, nicotine, and many other potentially important constituents (see Figure 2). The total smoke dose is positively related to the number of puffs taken per cigarette. However, total smoke dose might be changed by diluting the smoke with air or changing the number of available cigarettes. Alternatively, the smoke concentrations can be kept constant while changes are made in the concentration of nicotine delivered. This Section reviews these and several other strategies used to investigate some form of tobacco/nicotine dose manipulation and the resultant effects on cigarette smoking.

Control of Nicotine Intake

Among the most robust findings in research on cigarette smoking is the stability of nicotine intake that occurs from day to day within cigarette smokers. Several studies have collected blood samples from cigarette smokers while they are smoking their own cigarettes (Russell, Jarvis et al. 1980; Benowitz et al. 1983; Gori and Lynch 1985). This research has shown that blood levels of nicotine and cotinine among different cigarette smokers are stable and are relatively independent of the machine-estimated nicotine yield of the

cigarettes. Similarly, there are generally only modest correlations between the number of cigarettes smoked per day and resultant blood nicotine levels. This finding occurs because smokers consume different amounts of nicotine from their cigarettes, according to how the cigarettes are smoked. Figure 2 presents data from one of these studies.

To explain why nicotine intake is not simply determined by the machine-estimated nicotine yield of the cigarettes or the number of cigarettes smoked, many other aspects of smoking have been measured. This research is described in the remainder of this Section.

Smoke Concentration

The concentration of tobacco smoke delivered to the lung can be changed by dilution with air. Such dilution is an important means by which the low smoking-machine-estimated ratings (e.g., Federal Trade Commission ratings) of tar and nicotine are achieved in the so-called "light" or "ultra light" cigarettes (Kozlowski 1981, 1982, 1986, 1987). One way to study the possible effects of smoke dilution is to use the ventilated cigarette holders which have been marketed for persons who are trying to quit smoking. In principle, the smoker gradually reduces his or her level of dependence to nicotine by using holders of gradually increasing ventilation level. Three laboratory studies have evaluated the effects of such holders on cigarette smoking behavior (Henningfield and Griffiths 1980; Sutton et al. 1978; Martin et al. 1980). The results of all three were consistent: smoking was more intense at lower smoke concentrations and less intense at the highest concentration. In fact, in one of the studies, expired air CO levels were similar at all four concentration levels, indicating that the changes in smoking intensity were sufficient to defeat the holders' intended purpose of reducing the dose taken (Henningfield and Griffiths 1980). Using a somewhat different strategy, Zacny, Stitzer, and Yingling (1986) studied cigarette smoking with commercially available ventilated cigarettes. When the experimenter systematically blocked the filter vents of "ultra" low-yield cigarettes, there were decreases in puffs per cigarette, puff volume, and puff flow rate, and increases in interpuff interval.

These laboratory findings are consistent with findings obtained outside the laboratory when the cigarette butts of vented cigarettes are examined following smoking. Kozlowski, Rickert, Pope, and Robinson (1982) found that the cigarette butts taken from people who blocked the ventilation holes (often inadvertently) were more stained by tar and nicotine, reflecting less effective dilution and hence greater amounts of smoke delivery to the smoker. Data from a laboratory study suggest that 40 percent or more of smokers may inadvertently block the holes (Kozlowski, Rickert, Pope, Robinson,

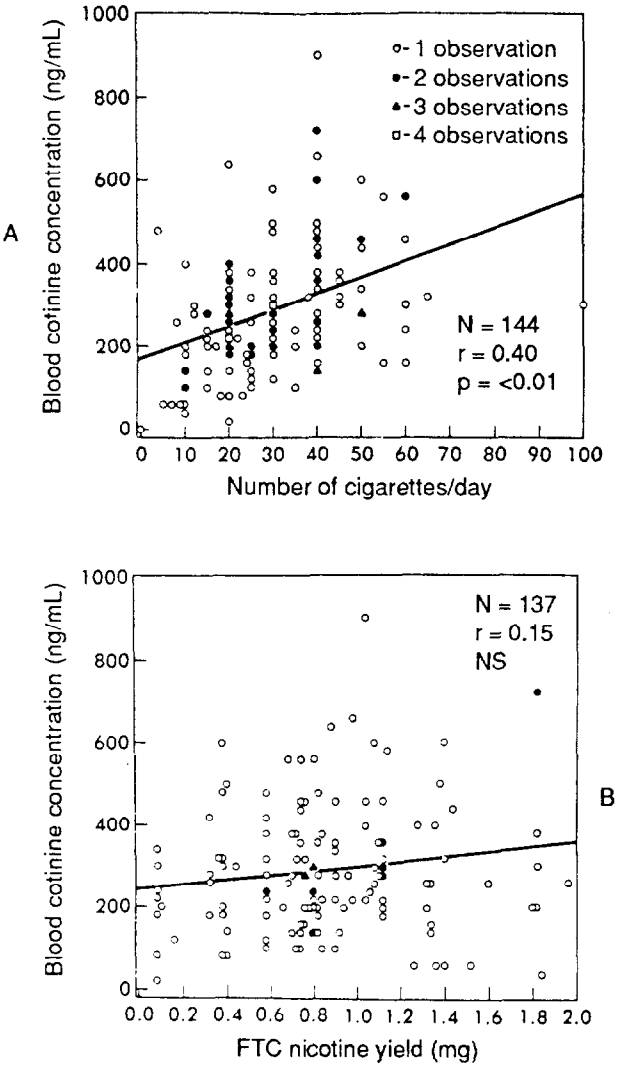

FIGURE 2.—Afternoon blood cotinine concentrations, compared by regression analysis with number of cigarettes smoked/day (A) and with U.S. Federal Trade Commission (FTC)-determined nicotine yield (B)

NOTE: The grouped smokers' values (observations 2–4) were so similar to individual values that plots overlapped. Total number of subjects in B is lower because data for a few subjects were incomplete. Morning blood cotinine concentrations (not shown) were on average slightly lower, but had similar correlations with number of cigarettes ($r=0.45$) and FTC yield ($r=0.06$).

SOURCE: Benowitz et al. (1983).

Frecker 1982). These findings imply that there is much greater exposure to cigarette smoke in the general population than one would expect based solely on the market share of ventilated cigarettes (US DHHS 1981; Kozlowski 1987).

Cigarette Length

When cigarettes are shorter, people smoke more of them (Ashton, Stepney, Thompson 1978; Goldfarb and Jarvik 1972; Gritz, Baer-Weiss, Jarvik 1976; Jarvik et al. 1978; Chait and Griffiths 1982b). Cigarette length may also affect how people smoke each cigarette. Ashton, Stepney, and Thompson (1978) found that smokers shortened their intervals between puffs and spent a greater proportion of time puffing on two-thirds-length cigarettes compared with full-length cigarettes. Russell, Sutton, and associates (1980) reported that smokers took relatively more puffs and left shorter butts when smoking shortened cigarettes. In another study, subjects smoking half-length cigarettes shortened the interval between puffs, but did not spend more time puffing on these cigarettes relative to full-length cigarettes (Chait and Griffiths 1982b). Puff duration and puff volume were inversely proportional to the length of the tobacco rod, even for the first puff of the cigarette (Chait and Griffiths 1982a; Nemeth-Coslett and Griffiths 1984a,b, 1985).

Cigarette Brand

Numerous studies have examined the effects of cigarette brand manipulations on cigarette smoking, and several reviews are available (Gritz 1980; Moss and Prue 1982; McMorrow and Foxx 1983). Such studies are of practical importance because smokers often switch to lower tar/nicotine yielding cigarette brands in an effort to reduce this exposure to toxins and to reduce their level of nicotine dependence (see Chapter VII). One finding of these studies is that the number of cigarettes smoked per day is only slightly increased when lower nicotine-yield brands are used. For this reason, it has been suggested that smokers switch to lower yield cigarette brands (1) to reduce exposure to smoke constituents and (2) to help them gradually reduce their dependence on nicotine (see discussion of these issues in US DHHS 1981 and in Chapter VII (nicotine fading)). However, as discussed earlier, several other studies indicate that there is little correlation between the nicotine rating of a cigarette and the plasma nicotine level of the smoker (Russell, Jarvis et al. 1980; Benowitz et al. 1983; Gori and Lynch 1985). Kozlowski (1981, 1982) has observed that increases of only one or two puffs per cigarette and possibly other more subtle changes in cigarette smoking (e.g., blocking ventilation holes and taking deeper inhala-

tions) may defeat the intended purpose of the brand-switching procedure.

Laboratory studies have provided information on the specific changes in smoking behavior that may reduce the intended impact of switching to lower yield brands of cigarettes. One confounding factor in such studies is that machine-estimated nicotine, tar, and CO yields do not necessarily change to the same degree or even in the same direction from one cigarette brand to the next (Tobacco Reporter 1985); thus, no definitive conclusions can be drawn about which specific smoke component was responsible for observed changes in smoking behavior. Nonetheless, some orderly and consistent findings emerge from a review of this literature. Several measures suggest that when tobacco smoke constituent ratings decline, smoking is more intense so that more smoke is delivered per cigarette; conversely, when tobacco smoke constituent ratings are higher, cigarette smoking becomes less intense (Frith 1971; Ashton, Stepney, Thompson 1979; Stepney 1981; Guillerm and Radziszewski 1978; Rawbone et al. 1978; Adams 1978; Creighton and Lewis 1978a; Ossip-Klein, Epstein et al. 1983; Russell et al. 1982; Ashton and Watson 1970; Epstein et al. 1981; Russell, Epstein, Dickson 1983; Tobin and Sackner 1982; Fagerström and Bates 1981; Woodman et al. 1987).

The consensus of the foregoing studies is that smokers tend to smoke in ways that minimize the effect of attempted reductions in nicotine intake; however, brand preferences can modulate nicotine intake. One study employing biochemical measures of smoke intake illustrated both of these phenomena (Benowitz and Jacob 1984). Subjects were permitted to smoke under each of three cigarette conditions: using their regular cigarette, using a higher nicotine-yield brand, and using a lower nicotine-yield brand. Subjects maintained significant nicotine intake under all three conditions, but the highest intakes of nicotine were with the subject's preferred brand. Nicotine intake from the lower nicotine-yield brands was somewhat lower than intake from the higher yield brands. Taken together, these studies indicate that brand switching may result in somewhat decreased levels of intake of nicotine and other constituents of tobacco smoke. However, because of compensatory changes in how cigarettes are smoked and in the number of cigarettes smoked, the decreases are substantially less than would have been predicted on the basis of the machine-estimated yield of the cigarettes.

Cigarette Yield of Nicotine

Research cigarettes which vary mainly in machine-estimated nicotine yield ratings but little in the yield of other constituents (e.g., tar, CO) have also been used in laboratory and nonlaboratory studies of cigarette smoking. This literature has been extensively reviewed (Russell 1971, 1976; Gritz 1980; Henningfield 1984; US DHEW 1979;

US DHHS 1981). The consensus of the literature indicates that as nicotine yield increases, the number of cigarettes smoked per day tends to decrease, although the converse relationship is not as robust (Russell 1979). Because few of these studies employed measures of smoking other than number of cigarettes smoked per day, the degree to which overall cigarette smoking behavior actually varied as a function of such manipulations may have been underestimated (Henningfield 1984).

Laboratory studies in which multiple behavioral measures of cigarette smoking were employed indicate that smoking is sensitive to nicotine dose manipulations. When cigarettes with higher nicotine yield ratings are smoked, there are decreases in measures such as puffs per cigarette, puff duration and puff volume, number of cigarettes, and expired air CO; and increases in interpuff and intercigarette interval (the specific measures were not identical for the three studies summarized) (Herning et al. 1981; Gust and Pickens 1982; McBride et al. 1984). These changes in smoking are consistent with the interpretation that intensity of smoking is inversely related to nicotine dose, indicating that compensatory changes in smoking could be affected by nicotine itself.

Urine pH

Because some nicotine is normally eliminated in the urine, manipulations of the rate of nicotine excretion might be expected to change cigarette smoking behavior (see Chapter II). Rate of renal excretion is partially determined by the acidity of the urine: lower pH values (higher acidity) increase the rate of nicotine excretion. One study showed that acidification of the urine of cigarette smokers resulted in small increases in cigarettes smoked per day, and alkalinization of urine was accompanied by only very small decreases in smoking (Schachter, Kozlowski, Silverstein 1977). A subsequent study in which urine pH was varied showed no change in cigarette smoking measures (Cherek, Mauroner, Brauchi 1982); another showed small but significant effects on nicotine intake in the expected direction (Benowitz and Jacob 1985).

The fact that there is a direct albeit weak relationship between rate of nicotine excretion and cigarette smoking has suggested to some that alkaline diets might be useful for persons trying to decrease their cigarette smoking (Fix and Daughton 1981; Fix et al. 1983; Grunberg and Kozlowski 1986). However, the relatively small amount of systemic nicotine which is eliminated by this route (approximately 2 percent in alkaline urine, 10 percent in urine without controlled pH) (Rosenberg et al. 1980; Benowitz and Jacob 1985; Chapter II) weakens its practical significance as a determinant of cigarette smoking behavior. The results of clinical studies suggest

that such therapies are not useful in the cessation of smoking (see also Grunberg and Kozlowski 1986; Schwartz 1987).

Tobacco Administration and Deprivation

When tobacco smoke itself is given or withheld, the tendency to smoke, as well as the way cigarettes are smoked, may be affected. Kumar and colleagues (1977) reported that pretreating smokers with a varying number of uniform puffs of tobacco smoke produced dose-related reductions in the subsequent number of puffs taken, volume per puff, and total puff volume during a 40-min period of smoking ad libitum. In a study of similar design, Chait, Russ, and Griffiths (1985) found that an increasing number of uniform pretreatment puffs decreased subsequent puffs per cigarette, cigarette duration, and total puff duration. Analogously, when the number of puffs available during any period of smoking (smoking "bout") during a given day was varied by the experimenter from 1 to 12 while the smokers were free to vary the interbout interval, the intervals between each smoking bout were directly related to the number of puffs that had been given (Griffiths, Henningfield, Bigelow 1982). These studies show that cigarette smoke intake is a function of time since the last cigarette or the smoke dose given at any smoking opportunity.

Whereas smoke pretreatment decreases several measures of cigarette smoke intake, other studies have found that deprivation for just 1 hr increases the tendency to smoke and elevates several measures of tobacco smoke intake (Henningfield and Griffiths 1979); furthermore, these effects were not due to "anticipation" by the subjects of the periods of smoke deprivation (Griffiths and Henningfield 1982). Several additional studies have confirmed that smoke deprivation increases one or more measures of cigarette smoking (Karanci 1985; Griffiths and Henningfield 1982; Zacny and Stitzer 1985; Epstein et al. 1981). Sutton and coworkers (1982) found a small, but statistically significant, positive correlation between time since the last cigarette and total puff volume on the subsequent cigarette. Similarily, when the interval between each smoking opportunity was varied from 7.5 to 120 min and subjects were free to take as many puffs per smoking bout as they pleased, the number of puffs per bout was directly related to the duration of the preceding interbout interval (Griffiths, Henningfield, Bigelow 1982). Restricting the number of cigarettes that may be smoked is another way to study tobacco deprivation. When smokers who on average smoked 37 cigarettes/day were permitted to smoke only 5 cigarettes/day, they consumed three times as much nicotine per cigarette compared with unrestricted smoking (Benowitz et al. 1986).

The results of studies of the effects of tobacco administration and deprivation on subsequent rates and patterns of cigarette smoking show that tobacco smoke can function as do other primary reinforc-

ers such as food, water, and dependence-producing drugs (Thompson and Schuster 1964). Such studies in themselves, however, do not reveal which of the many tobacco smoke constituents are critical. The next two sections will examine evidence that specific manipulations of nicotine and nicotine antagonists can produce analogous changes in cigarette smoking.

Nicotine Pretreatments

One of the basic ways to demonstrate that a psychoactive drug is controlling behavior is to determine if pretreatment with the drug leads to decreases in the amount subsequently taken. Such findings have been obtained with a variety of dependence-producing drugs (e.g., Griffiths, Bigelow, Henningfield 1980; Chapter V), and the strategy has been used to study the role of nicotine in cigarette smoking. These studies have shown that nicotine pretreatment by a variety of routes decreases the amount and/or intensity of subsequent cigarette smoking although the specific measures that have been reportedly affected vary across studies. It is possible that differences across studies reflect variations in sensitivity of measurement techniques and in the measures used.

Cigarette smokers may be pretreated with nicotine by giving them nicotine polacrilex gum to chew. The gum is available in similar tasting nicotine dose levels of 2 or 4 mg/piece. A similar tasting placebo preparation with no nicotine is also available. (In the United States, the placebo and 4-mg dose are only available for research.) With various combinations of nicotine gum doses it is possible to provide a wide range of dose levels. In one study, the chewing of nicotine polacrilex gum produced a dose-related (dose range = 0 to 8 mg nicotine) decrease in cigarette consumption during subsequent 90-min cigarette smoking sessions: Total puffs, total cigarettes, and expired-air CO levels were inversely related to nicotine dose; desire to smoke was also inversely related to dose but this effect varied considerably and was not statistically reliable (Nemeth-Coslett et al. 1987). Comparable findings have been obtained in several other studies, although dose manipulations were not as extensive as in the former study (Kozlowski, Jarvik, Gritz 1975; Nemeth-Coslett and Henningfield 1986; Brantmark, Ohlin, Westling 1973; Russell et al. 1976; Herning, Jones, Fischman 1985). Another study showed that nicotine given in capsule form also reduced subsequent cigarette smoking (Jarvik, Glick, Nakamura 1970), although the low dose and poor systemic absorption of nicotine given by this route (see Chapter II) required that much higher dose levels be given (10 mg).

Two studies have also demonstrated that intravenous (i.v.) administration of nicotine decreases cigarette smoking (Lucchesi, Schuster, Emley 1967; Henningfield, Miyasato, Jasinski 1983). Another study found no change in smoking following i.v. nicotine infusions (Kumar

et al. 1977); however, the dose (equivalent to about 1.7 mg, given in 10 divided doses over 10 min) was probably inadequate, as suggested by results of other studies (Nemeth-Coslett et al. 1987). The finding that even i.v.-delivered nicotine can reduce subsequent cigarette smoking confirms that neither the tobacco vehicle nor the oral/respiratory route is necessary for nicotine to control behavior. The overall consistency of findings using a variety of forms of nicotine pretreatment is evidence for a specific effect of nicotine as a determinant of cigarette smoking.

Nicotine Antagonist Pretreatments

Another way to evaluate the specific role of nicotine as a determinant of rate and pattern of cigarette smoking is to administer drugs that block the effects of nicotine on the nervous system. Nicotine antagonists (ganglionic blockers) are available as drugs (e.g., pentolinium and hexamethonium) that do not readily enter the brain but are active in the peripheral nervous system, and as drugs (e.g., mecamylamine) that do enter the brain and thus work in both the peripheral and central nervous system (CNS) (Taylor 1985b). In theory, such drug administration should produce effects that are analogous to those that would be expected if the nicotine dose of cigarettes was decreased: that is, smoke intake should increase. Moreover, if smoke intake increases, but only when the centrally acting antagonist is given, such data would suggest the critical involvement of the effects of nicotine in the brain.

Three studies showed that pretreatment of smokers with mecamylamine produced increases in cigarette smoking that resembled those expected if the nicotine dose of the cigarettes had been decreased (Stolerman et al. 1973; Nemeth-Coslett et al. 1986a; Pomerleau, Pomerleau, Majchrzak 1987). In each of these studies, the short-term effect of the nicotine antagonists was studied. Similarly, mecamylamine pretreatment increased the preference for high nicotine-yield cigarette smoke (apparently by reducing its nicotinic effects) when subjects were tested with a device which blends smoke from high and low nicotine-yield cigarettes (Rose, Sampson, Henningfield 1985). The role of nicotine action in the brain was demonstrated in the study by Stolerman and colleagues (1973) in which a nicotine blocker (pentolinium) that does not readily enter the brain produced no effects on cigarette smoking.

Effects of Nonnicotinic Drugs on Cigarette Smoking

In addition to nicotine and nicotine antagonists, the effects of other psychoactive drugs on cigarette smoking have been studied in the laboratory. Such studies are important insofar as they constitute drug-interaction studies whereby it may be determined if the

behavioral and physiological actions of nicotine are altered as a function of pretreatment with other drugs. In addition, studies of interactions of nicotine with other dependence-producing drugs are important because tobacco use generally precedes and accompanies use of many other dependence-producing drugs (Chapter V). Several classes of psychoactive drugs have been administered in studies in which cigarette smoking was specifically measured. In general, the results permit a categorization of these drugs into two groups: (1) those drugs that produce increases in smoking under standard test conditions, and (2) those drugs that produce little reliable effect on cigarette smoking under standard test conditions.

Sedatives, opioid agonists, and psychomotor stimulants have been shown capable of producing robust and dose-related increases in cigarette smoking. Specifically, alcohol (ethanol) has been shown to increase cigarette smoke intake (Griffiths, Bigelow, Liebson 1976; Henningfield, Chait, Griffiths 1984; Nil, Buzzi, Bättig 1984; Mintz et al. 1985; Mello et al. 1980b). In a study in which alcohol was found to increase smoking in all of five alcoholic subjects tested, pentobarbital (a depressant) was found to increase smoking in the two subjects with extensive histories of barbiturate use (Henningfield, Chait, Griffiths 1984). The effects of alcohol and pentobarbital were most robust in heavier drinkers and alcoholics (Henningfield, Chait, Griffiths 1983, 1984). The opioid agonists, heroin and methadone, increase cigarette smoking in opioid users (Mello et al. 1980a; Chait and Griffiths 1984). Methadone produced dose-related increases in number of cigarettes and puffs, and in puff duration in methadone-maintained smokers (Chait and Griffiths 1984). Analogously, number of cigarettes smoked per day gradually decreased as methadone-maintained clients had their daily methadone doses decreased over several weeks (Bigelow et al. 1981). Finally, the psychomotor stimulant *d*-amphetamine increases a variety of measures of cigarette smoking (Henningfield and Griffiths 1981; Chait and Griffiths 1983).

Three other drugs have been studied and found to produce little reliable effect on cigarette smoking. Caffeine is of interest because it might be predicted to either increase smoking by its general stimulant (amphetamine-like) effects (Rall 1985) or to decrease smoking by serving as a substitute for some of nicotine's stimulant effects (Kozlowski 1976). Laboratory studies, however, have found the effects of caffeine administration on cigarette smoking to be weak and inconsistent: two studies showed no reliable effect (Chait and Griffiths 1983; Nil, Buzzi, Bättig 1984), another showed weak decreases in smoking (Kozlowski 1976), and a fourth showed weak increases in smoking following caffeine administration (Ossip and Epstein 1981).

The opioid antagonist naloxone (naloxone blocks effects of heroin-like opioids) is another drug of interest because of the possible role of endogenous opioids as mediators of some of the effects of nicotine (Chapter III; Pomerleau and Pomerleau 1984). In a test paradigm in which several drugs have been shown to produce orderly effects on cigarette smoking (Griffiths and Henningfield 1982), naloxone produced no consistent changes in cigarette smoking over a wide range of dose levels (Nemeth-Coslett and Griffiths 1986). Another study of the effect of naloxone which employed a single dose found a reduction in smoking (Karras and Kane 1980). No clear reconciliation of these disparate findings is evident. Finally, marijuana pretreatment was found to produce no reliable effect on tobacco intake (Mello et al. 1980b; Nemeth-Coslett et al. 1986b) or on the way cigarettes were smoked (Nemeth-Coslett et al. 1986b).

Effects of Nonnicotine Constituents of Tobacco Smoke and Citric Acid Aerosol

Chemicals presumed to act primarily in the respiratory tract and not in the central nervous system may also affect smoking. The region of the trachea just below the larynx is assumed to be a site of some cigarette smoke related sensations (Cain 1980). This site corresponds to the region 2 cm below the narrow opening of the larynx where particles entering the trachea change direction (Chan and Schreck 1980).

The components of cigarette tar and volatile gases in smoke contribute to the taste, olfactory, and tracheobronchial sensations elicited by cigarette smoke. In fact, minimal levels of tar are held by tobacco manufacturers to be important to maintain product satisfaction in smokers (Tobacco Reporter 1985; Gori 1980). Besides its causal role in lung cancer and other diseases (US DHHS 1982, 1983, 1984), tar may function to mask the harshness and irritation of nicotine (Herskovic, Rose, Jarvik 1986). Consistent with this hypothesis, nicotine aerosols delivering doses of nicotine similar to those in mainstream cigarette smoke are rated as extremely harsh and irritating by cigarette smokers (Russell 1986). Similarly, some gaseous components of smoke, such as acrolein and formaldehyde, are irritating and could also contribute to the tracheobronchial sensations elicited by smoke (Lundberg et al. 1983).

Levels of tar and other constituents may also contribute to brand preference and, conversely, to the difficulty in finding readily acceptable substitutes for the cigarettes normally smoked by individuals. For example, a nonmentholated cigarette may not be a desirable substitute for a mentholated one. Moreover, when given cigarettes made of lettuce or cocoa leaves, smokers complain about the unpleasant smell and taste (Goldfarb, Jarvik, Glick 1970; Herskovic, Rose, Jarvik 1986). Tobacco research cigarettes are often

found to be less palatable than commercial brands (Benowitz, Kuyt, Jacob 1982), indicating the importance of specific tobacco blends and/or additives in determining taste and brand preferences.

The precise nature of the sensations critical to smoking satisfaction has not been elucidated, and the relative roles of taste, olfaction, and tracheobronchial sensations are not clear. One way to assess the importance of local respiratory sensations in the subjective response to cigarette smoke is to block these sensations with a short-acting topical anesthetic. Two studies have used inhalation of a 4-percent lidocaine aerosol and mouth rinses and gargling with lidocaine solutions to assess the importance of airway sensations to cigarette smokers (Rose et al. 1984, 1985). In both studies, the desirability of puffs was decreased by local anesthesia of the respiratory tract. Additionally, the decline in reported craving for cigarettes that usually occurs after smoking was diminished by local anesthesia.

A study was also conducted in which smokers inhaled a refined tobacco smoke condensate (Rose and Behm, in press). The condensate produced a low overall nicotine yield (about 0.2 mg/10 puffs), while maintaining a higher ratio of nicotine to tar and a larger particle size than that of conventional cigarette smoke. Smoke generated in this fashion was rated as stronger and harsher than smoke of equivalent nicotine content delivered by smoking a conventional low-tar and low-nicotine cigarette (Rose and Behm 1987). The subjects also reported significantly greater satisfaction and diminished desire to smoke additional cigarettes after inhaling puffs of refined smoke compared with conventional low-nicotine cigarette smoke (Rose and Behm 1987). These studies demonstrate that local sensory effects of smoke may influence the short-term subjective responses to smoking.

The inhalation of aerosols containing citric acid is a standard method of eliciting coughing in human subjects (Pounsford and Saunders 1985). One study found that smokers inhaling puffs of a nebulized 15 percent aqueous solution of citric acid reported sensations of strength and harshness comparable to those produced by their own cigarette brand and considerably stronger than those elicited by an "ultra" low-tar, low-nicotine cigarette (Rose and Hickman 1987). Moreover, some pleasure was reported to be associated with these sensations, and desire for cigarettes was decreased, suggesting that mild irritation of the respiratory airways may be involved in satiation of smoking behavior and may have a role in smoking cessation efforts (Henningfield 1987c; Chapter VII).

Nicotine: Psychoactivity, Reinforcing and Related Behavioral Mechanisms of Nicotine Dependence

As the preceding sections have shown, cigarette smoking is an orderly behavioral and pharmacologic process clearly involving

maintenance of the desired levels of nicotine in the body. These data are sufficient to label tobacco use as a form of drug self-administration in which the role of nicotine in controlling tobacco self-administration functions as do morphine, ethanol, and cocaine in the use of opium-derived products, alcoholic beverages, and coca-derived products, respectively. However, the question may be asked whether the behavior-controlling pharmacologic properties of nicotine are similar to those of prototypic dependence-producing drugs when evaluated in standard laboratory tests. More specifically, the scientific question is whether nicotine itself shares critical dependence-producing properties with drugs such as morphine, cocaine, and alcohol. Standardized testing procedures can be used in both animal and human studies to objectively determine if a drug is dependence producing. These procedures, as well as a review of how addicting drugs control behavior, is presented in Chapter V. Chapter V also presents data obtained when drugs such as morphine, cocaine, and alcohol are tested by identical procedures.

In brief, four general kinds of behavior-modifying drug effects can be differentiated on the basis of the test procedure used. These drug effects are discussed in Chapter V and include the following: (1) Drugs may produce *interoceptive* stimulus effects; that is, they can produce effects that a person or animal can distinguish from the nondrug state. Although not identical in meaning, the following terms are often used to designate interoceptive drug effects: "psychoactive," "discriminative," "subjective," "self-reported." (2) Drugs may serve as *positive reinforcers* or *rewards*, the presentation of which produces repetition and strengthening of the behaviors which led to their presentation, i.e., "drug self-administration" or "drug seeking." (3) Drugs can serve as *unconditioned stimuli*, in which case they may directly elicit various responses; these responses may subsequently be elicited by stimuli which are associated with the drug (i.e., conditioned stimuli), including the presence of environmental, or even internal, cues. (4) Drug administration or abstinence can also function as *"punishers"* or *aversive* stimuli.

This Section will present data from studies of nicotine with each of the four testing procedures mentioned above. The convergence of findings from several distinct approaches provides compelling evidence that nicotine is a drug that can effectively control behavior, including behavior leading to its own ingestion (i.e., dependence or addiction).

Interoceptive, Discriminative, and Subjective Effects of Nicotine

Ingested chemicals can serve as stimuli by actions on either peripheral or centrally located receptors or by indirect effects mediated through the release of various biochemicals or neurohor-

mones. In general, the term "psychoactive" is reserved for those drugs whose discriminative effects are known to result from their actions in the brain. As described by Lewin (1931) and others (Thompson and Unna 1977) it is, in part, the nature of the discriminative stimulus effects of a drug within the body that sets the dependence-producing drugs apart from other non-nutritive substances. As shown in Chapter II, all commonly used forms of tobacco are effective means of delivering nicotine to the blood from which it is rapidly transported to the brain. Research with animals has shown that nicotine produces distinct effects in the central nervous system (CNS). In addition, nicotine has diverse peripheral and hormonal actions that could serve to intensify its CNS stimulus properties. The biochemical mechanisms of these effects are discussed in Chapter III.

Three procedurally distinct methods have been used to characterize the stimulus properties of nicotine and will be discussed in the following sequence: (1) discrimination testing in animals and humans, (2) assessing subjective effects in humans, and (3) testing for state-dependent learning effects in humans. Each method has been used to help characterize the stimulus properties of a variety of drugs including nicotine (Chapter V).

Drug Discrimination Testing in Animals

Animal studies of nicotine discrimination show that nicotine produces reliable effects that are readily identified by the subjects. Such studies indicate that fundamental biobehavioral mechanisms mediate the psychoactive properties of nicotine in humans, and that such effects are not unique to human psychological processes. These data also have implications for understanding and treating tobacco dependence and are summarized below.

Specificity of the Nicotine Stimulus

Although dependence-producing drugs may overlap, to some degree, in the nature of their effects on mood and feeling, each drug class and sometimes drugs within a class produce unique effects. As this Section shows, nicotine also produces some effects that permit it to be distinguished from most other psychoactive drugs. These studies are also useful for testing new drugs that are thought to produce nicotine-like effects.

Rats can learn to accurately discriminate nicotine from placebo regardless of the route of administration as long as the nicotine reaches the brain. Most researchers have utilized the subcutaneous (s.c.) route of administration (Rosecrans and Meltzer 1981); however, more recent studies have incorporated other routes of nicotine administration and have found that rats could learn to discriminate

nicotine when given nicotine by gavage (oral tube) in a dose of 0.5 mg/kg (Howard and Craft 1987). Oral nicotine-trained rats generalized to nicotine administered via either the s.c. or transdermal routes (nicotine solution was applied to a 1.5-cm circular area on the shaved back of the rat). There was little difference in dose potency between the oral and s.c. routes; however, the transdermal route was much less potent and required eight times the oral dose to establish equivalent response patterns. Taken together, the results of these studies showed that nicotine given by a variety of routes produces time- and dose-related discriminative effects.

Several studies have compared nicotine with a variety of drugs by these drug discrimination testing procedures (Rosecrans and Meltzer 1981; Stolerman et al. 1987). Early research involved testing a wide variety of chemicals. These studies showed that nicotine-trained rats did not generalize to drugs of other classes such as the opioids, barbiturates, or hallucinogens (Rosecrans and Meltzer 1981). Of special interest was the prototypical stimulant *d*-amphetamine, because nicotine also has a variety of stimulant-like actions (Rall 1985). When nicotine-trained rats were tested with amphetamine, however, they only partially generalized to nicotine. In another study, Schechter (1981) observed higher levels of amphetamine generalization to nicotine in a group of rats trained to discriminate amphetamine from pentobarbital. Thus, nicotine may have some amphetamine-like effects which are unmasked under certain conditions.

Oxotremorine and arecoline are agonists of the cholinergic nervous system, but these drugs activate muscarinic, and not nicotinic, cholinergic receptors (Gilman et al. 1985). Consistent with the mechanisms of action of these cholinergic drugs are the findings that neither oxotremorine nor arecoline generalized to nicotine in nicotine-trained animals (Rosecrans and Meltzer 1981).

Nicotine analogs and metabolites have also been studied with the discrimination paradigm (Rosecrans and Chance 1977; Stolerman et al. 1987). Such research can help reveal the extent, if any, of the role of these nicotine-related or nicotine-derived chemicals in determining the nature of the discriminative effects that follow nicotine administration. In rats trained to discriminate 100 μg/kg of nicotine, the analogs cytisine and anabasine generalized to nicotine. The alkaloid nornicotine generalized partially to nicotine. Cotinine, the major metabolite of nicotine, was observed to generalize to nicotine only when the cotinine was given intraventricularly in relatively high doses to rats trained to discriminate relatively low dose levels (100 μg/kg) of nicotine. These data show that although metabolites of nicotine may share some stimulus properties with nicotine, the degree of generalization is weak, suggesting that the discriminative

stimulus effects of nicotine are mainly due to nicotine itself and not to the metabolites.

Synthetic analogs of nicotine have also been evaluated for their possible nicotine-like properties in discrimination studies (Rosecrans, Kallman, Glennon 1978; Rosecrans et al. 1978). Of the several compounds tested, only one, 3-methyl-pyridylpyrollidine, a chemical isomer of nicotine, was observed to generalize to the nicotine stimulus in nicotine-trained rats. This compound was observed to be 8 to 10 times less potent than nicotine. Its effects were significantly antagonized (reduced or blocked) by mecamylamine, which also antagonizes the stimulus generated by both S– and R–nicotine; the naturally occurring tobacco constituent, S–nicotine, is also 8 to 10 times more potent as a stimulus than R–nicotine. The results of these investigations indicate that the stimulus properties of nicotine are highly specific.

A finding relevant to pharmacologic treatment efforts (see Chapter VII) involved discrimination studies with lobeline (a constituent in several over-the-counter aids for quitting smoking). Lobeline is an alkaloid with some nicotine-like ganglionic effects in the peripheral nervous system (Gilman et al. 1985). Rosecrans and Chance (1977) found that lobeline was neither discriminated as nicotine nor did it block nicotine discrimination in nicotine-trained rats. These results do not support the use of lobeline-containing compounds as treatment aids for cigarette smoking (see also Schwartz 1987; Chapter VII).

Peripheral Versus Central Discriminative Stimulus Effects of Nicotine

The degree to which the stimulus is generated via peripheral rather than central nervous system (CNS or brain) actions is also important in understanding the nature of the nicotine stimulus. As discussed in Chapter III, nicotine has many peripheral autonomic nervous system (ANS) effects which might feed back to the CNS, thereby indirectly generating or contributing to stimulus effects. Thus, changes in blood pressure, heart rate, body temperature, and hormone release could be potential mediators of the effects. Several approaches have been utilized to address the role of peripheral actions of nicotine in the generation of the discriminative stimulus. One approach is to attempt to block nicotine with an antagonist not able to enter the CNS.

In one study, animals were trained to discriminate a dose of nicotine (Rosecrans and Chance 1977). Then they were pretreated with a series of nicotinic cholinergic antagonists and with muscarinic cholinergic antagonists. After pretreatment with an antagonist, the animals were retested with the training dose of nicotine. Mecamylamine, a centrally and peripherally acting nicotine antago-

nist, was the only drug observed to completely block the nicotine stimulus. As the dose of this antagonist was increased, percent correct responses on the nicotine-correct lever, after the injection of 200 or 400 μg/kg of nicotine, decreased to placebo response levels, indicating a complete antagonism of the nicotine stimulus. In a similar study, Stolerman, Pratt, and Garcha (1982) increased the nicotine dose in an attempt to overcome the actions of mecamylamine: the blockade was not overcome by any dose of nicotine. Thus, these data suggest that mecamylamine is not a competitive antagonist (blocking at the receptor itself) but rather may functionally antagonize nicotine's effects through another mechanism (Stolerman et al. 1987).

In other studies, a 331 μg/kg dose of mecamylamine antagonized the stimulus effects of 200 μg/kg of nicotine, while 835 μg/kg was required for similar antagonism of the 400 μg/kg dose of nicotine (Rosecrans and Meltzer 1981). All such studies found that the peripherally acting nicotinic antagonist, hexamethonium, did not affect nicotine discriminations. The muscarinic antagonist, atropine, was also without effect. The possible relationships of the nicotine stimulus to brain norepinephrine and 5-hydroxytryptamine (serotonin or 5-HT) systems were also investigated through the use of the appropriate antagonists/agonists. Similarly, a quaternary analog of nicotine, which does not enter the brain, was evaluated and found to produce no evidence of generalization in nicotine-trained rats (Rosecrans et al. 1978). Such studies do not support the involvement of peripheral systems in the generation of the nicotine stimulus.

Another strategy used to investigate the central nature of the nicotine stimulus compared concentrations of nicotine in the brain with the resulting stimulus effects of nicotine (Rosecrans and Chance 1977). It was assumed that if nicotine's stimulus effects are mediated in the brain, then such effects should be related to brain levels of nicotine. This hypothesis was confirmed. In fact, it was found that before nicotine functions as a stimulus, it must achieve a minimal drug level in the brain. In addition to relating drug level in the brain to the stimulus effect induced by nicotine, Rosecrans and Chance (1977) showed that systemically administered nicotine generalized to nicotine administered intraventricularly. Taken together, the foregoing studies show that the nicotine-generated discriminative stimulus is dependent on the actions of nicotine at central nicotine receptors in the brain.

Drug discrimination research has also examined the stimulus properties of the muscarinic cholinergic agonist, arecoline. Arecoline is a constituent of the betel nut mixtures commonly chewed in the East Indies (Taylor 1985a). Three approaches have been utilized to investigate the stimulus properties of arecoline. In the first study, arecoline served as a discriminative stimulus and thereby assumed

control of behavior (Rosecrans and Meltzer 1981). These effects of arecoline were blocked by pretreatment with the muscarinic antagonist, atropine, while the quaternary compound, methyl atropine (which does not readily cross the blood-brain barrier), was ineffective. These results indicate that the stimulus can also be exerted via muscarinic stimulation and confirm that the discriminative stimulus properties of muscarinic agonists, like those of nicotinic agonists, are centrally mediated. Additional studies indicated that mecamylamine was not able to antagonize the stimulus effects of arecoline (Rosecrans and Meltzer 1981). Finally, it was found that rats could be trained to discriminate between the muscarinic and nicotinic agonists, arecoline and nicotine. Thus, there appear to be two independent central cholinergic receptor systems (muscarinic and nicotinic), each of which can exert stimulus control over behavior when appropriately stimulated. These findings have been confirmed by Stolerman and colleagues (1987).

Interactions with Noncholinergic Neurons

In a preliminary study (Takada et al., 1988) two nicotine-trained squirrel monkeys recognized beta-carboline as nicotine. Beta-carboline induces symptoms resembling anxiety in animals; these symptoms can be reduced by administration of the anxiolytic, diazepam (Shephard 1986). In addition to this observation, Colpaert (1977) reported that nicotine can antagonize the diazepam cue, and Heath, Porter, and Rosecrans (1985) noted that nicotine antagonized the effects of diazepam on punished responding in rats. Mecamylamine was also found to attenuate the nicotine-induced antagonism of diazepam's antianxiety effect. Harris and coworkers (1986) found that metrazol (a convulsant) partially generalized (35 percent) to nicotine when tested in the discrimination paradigm in nicotine-trained animals. A greater degree of generalization of the metrazol cue to nicotine (50 percent) was observed 48 hr after the cessation of a 21-day chronic nicotine regimen in rats trained to discriminate metrazol (5 mg/kg) from saline; these generalizations were not antagonized by mecamylamine. Harris and colleagues (1986) suggested that the generalization of metrazol to nicotine was a function of a nicotine abstinence-induced withdrawal syndrome resembling anxiety. These studies suggest that nicotine may act at central receptors capable of eliciting a stimulus cluster which induces anxiety (Chapter III).

Subjective Effects of Nicotine in Humans

The extensive amount of nicotine discrimination research using a variety of animal species and several routes of administration confirms that nicotine is a potent drug that can induce alterations in